COMMENTARY

by Bernard Dixon

NEW VIRAL WEAPONS AGAINST PLANT INFECTIONS

Unlike the negative feedback operating in so many biological systems, that which a columnist receives from readers is invariably positive. While people respond to topics they find interesting, they ignore boring ones. And when there is a torrent of positive feedback, as followed my recent discussion of bacteriophage therapy (BIO/TECHNOLOGY, 1983, 1:777) one has clearly located a subject of unusual significance.

It's particularly exciting too when a letter arrives that gives an emerging story an altogether new dimension. So I'm more than grateful to Jeffrey Davies, head of virus research at the John Innes Institute in Norwich. He has written to suggest that viruses could prove as great a boon in attacking bacterial infections of plants as in treating the intestinal diseases that are being studied by H. Williams Smith and Michael Huggins at Houghton Poultry Research Station. Certainly a perusal of the recent literature indicates that there is tremendous potential here that has been only marginally explored.

To begin with a paradox: until a few years ago, some of the plant infections now seen as possible candidates for control by viruses were actually thought to be caused by viruses. They include clover phyllody and several "yellows" diseases, recently recognized as being due to mycoplasmas—tiny organisms, much smaller than most conventional bacteria and lacking a rigid cell wall. Because they have an etiology like those of infections produced by persistent viruses, it's likely that many more so-called virus diseases of plants are instead attributable to mycoplasmas. Devilishly difficult to isolate, mycoplasmas are not at all easy objects for laboratory investigation, and efforts to attack them with antibiotics have brought mediocre rewards.

But mycoplasmas do seem vulnerable to viruses resembling the phages that invade larger, conventional species of bacteria. One that has been studied closely in Dr. Davies's department is *Spiroplasma citri*, the cause of citrus stubborn disease and comparable infections in a wide range of herbaceous plants. Some years ago his colleague Dr. P. G. Markham and others injected the spiroplasma into leafhoppers, so that these sap-sucking insects would in turn infect the Madagascar periwinkle plant, in which the disease could be conveniently studied. Maintained ever since by continuous grafting every two months, the helical-shaped spiroplasma always triggers off the same destructive sequence of events. Three to four weeks after grafting, the periwinkle foliage becomes yellow. New leaves are greatly reduced in size. The flowers then abort, a severe wilt develops, and after 6 to 10

weeks the plant dies.

The starting point for the John Innes team's growing belief in a possible method of curing this and related infections was the observation that cultures of *S. citri* often contained virus-like particles. It was a puzzling observation, however, because although these "viruses" turned up frequently in laboratory cultures, they were never seen in association with spiroplasmas inside the cells of ailing plants. So Dr. Markham and his group decided to study their biological significance, and especially what effect if any the viruses had on the spiroplasmas' capacity to ravage healthy plants.

A breakthrough in solving this technically demanding problem came when Markham infected a periwinkle, not by using leafhoppers, but by grafting onto it a cutting he had infiltrated with spiroplasmas. Three months later, the plant began to exhibit symptoms—but unusually mild ones, with only light yellowing and no wilting. As reported in *Annals of Applied Biology* (101:85), electron microscopy of the plant's cells then revealed spiroplasmas that were distorted and swollen, together with innumerable virus-like particles. Resembling phages using bacteria to replicate themselves, some of these "viruses" could be seen attached by short tails to the spiroplasmas. Others appeared to be in the process of budding from their host cells. Corresponding sections from periwinkle plants with full-blooded symptoms showed normal, helical spiroplasmas without predatory viruses.

Why one research group should have uncovered evidence of virus attack *in vivo*, where others before them had failed, is not entirely clear. Presumably, avoidance of an insect vector affected the subsequent production of virus. And as Dr. Markham and his colleagues point out, "it would not be surprising if spiroplasmas which support a productive virus infection had substantially reduced pathogenic capabilities and were transmitted with much lower frequency than those which are uninfected or harbouring non-productive latent virus."

Whatever the explanation for their success, the researchers decided next to adopt and adapt methods parallel with those employed in phage research. They grew lawns of spiroplasmas in glass dishes and inoculated them with filtered sap from the mildly-diseased plant. Result: the lawns developed clear zones, similar to the plaques that appear after phages are added to cultures of bacteria. And when spiroplasmas containing virus were introduced into plants already infected with spiroplasmas alone, the symptoms of disease were alleviated considerably. That was the clinching evidence that has convinced Markham and Davies of the very real opportunity for exploiting such viruses as weapons to be deployed against plant infections.

The only negative aspect to this in-

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triguing story of botanical detection is that its next chapter has yet to be written. Having published details of some of their experiments, and taken out two patents on the method of disease control that the results suggest, the John Innes researchers have been unable, for financial reasons, to move ahead as vigorously as they might have wished. Considering the unusually intractable nature of plant diseases caused by mycoplasmas and spiroplasmas—and the likelihood that lots of others remain to be recognized—this is a surprising inactivity, to say the least. ■

FINAL WORD (Continued from page 280)
of the world) to “make, use, and sell” all the human serum albumin eventually produced under the contract. However, without considering the entire context of our research and development strategy, the article distorted the implications of that license provision.

As a corporation, Genex has chosen not to enter pharmaceutical production. A young company, we can afford neither the many years of clinical trials nor the extensive capital commitment necessary to withstand the regulatory delays in taking a new drug to market. Thus, our strategy for proprietary product development pertains to the less regulated area of fine chemicals. Yet, the homogeneous nature of our technology enables us to apply our expertise to developing pharmaceutical products for others, including both American and foreign firms. We gain royalties over the long-term, and the immediate profits from client-sponsored projects help defray our own research costs toward the industrial applications of biotechnology that are of proprietary interest to us.

Also worthy of note here is the fact that a largely R&D-

dependent industry, such as biotechnology, is in great need of start-up and sustaining capital in its early years. In these pioneering years of the biotechnology industry, the availability of venture capital in the United States has depended heavily on industrial R&D contractual commitments. American industry was initially not as willing to fund R&D in the new biotechnology, but contracts did come from foreign companies willing to risk their R&D funds on what was then unproven technology. In turn, American venture capitalists were eager to provide equity financing to those companies capable of demonstrating both scientific and business acumen. Thus, those early international contracts resulted both directly and indirectly in the pivotal funds that built our industry.

It is true that other nations have chosen highly directed and visible strategies for technological development. For example, Japan is coordinating, through its Ministry of International Trade and Industry, a major effort to bring the benefits of biotechnology to its industrial processes. However, this strategy represents a difference in method of research funding from the United States—not a grabbing of the best of U.S. technology. Foreign countries often coordinate their research efforts in a way quite different from the more fragmented approach that we in the United States choose.

Indeed, our federal system of funding basic research offers significant advantages in achieving technological innovation. It is a system based not so much on concerted efforts and directed research (as in Japan and other countries), but on the establishment of priorities and a fostering of competitive roles among basic research scientists and industry. That this system works is witnessed by an extraordinary success of U.S. scientists in winning Nobel prizes, and the entrepreneurial fervor with which American industry exploits technological innovation in the marketplace. This innovative ability we Americans demonstrate regularly is not as evident in those societies that habitually borrow from the technology of others.

Problems that are arising and will arise from international technology are important policy questions. The debate over various proposals to limit or prohibit export of high technologies—a debate most timely with the expiration of the Export Administration Act of 1979—should be heard in the totality of all the issues, including the perspectives outlined here.

Export trade policies that aim at “protecting” U.S. science are unlikely to provide effective leverage. More likely, they have the potential for closing the door to the important “transfer” aspect of high technology industries and allowing our competitors greater success. The challenge in this country is to foster our system of innovation and keep our technology at the leading edge of worldwide competition. Export controls, in that regard, will hurt more than help. ■

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